PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference G63873PC	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/011860	International filing date *(day/month/year)* 20.10.2004	Priority date *(day/month/year)* 20.10.2003
International Patent Classification (IPC) or national classification and IPC C07K14/47, C12N9/16, G01N33/53, A61K38/43, C07K16/42		
Applicant F. HOFFMANN-LA ROCHE AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.04.2005	18.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Smalt, R Telephone No. +31 70 340-4275

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/011860

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-122 as originally filed

Sequence listings part of the description, Pages

1-9 as originally filed

Claims, Numbers

1-42 received on 13.05.2005 with letter of 03.05.2005

Drawings, Sheets

1/9-9/9 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19 and 35, partially

because:

☒ the said international application, or the said claims Nos. 19 and 35, partially relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-42
	No:	Claims	1,2
Inventive step (IS)	Yes:	Claims	3-6,8-42
	No:	Claims	1,2,7
Industrial applicability (IA)	Yes:	Claims	1-18,20-34,36-42
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

1. The following **documents** (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: CHENG MANGENG ET AL: "The p21Cip1 and p27Kip1 CDK 'inhibitors' are essential activators of cyclin D-dependent kinases in murine fibroblasts" EMBO (EUROPEAN MOLECULAR BIOLOGY ORGANIZATION) JOURNAL, vol. 18, no. 6, 15 March 1999 (1999-03-15), pages 1571-1583, XP002273562 ISSN: 0261-4189

D2: LABAER JOSHUA ET AL: "New functional activities for the p21 family of CDK inhibitors" GENES AND DEVELOPMENT, vol. 11, no. 7, 1997, pages 847-862, XP0008028702 ISSN: 0890-9369

D3: WO 03/063581 A (MALEK NISAR P ;FRED HUTCHINSON CANCER RES CT (US); ROBERTS JAMES M) 7 August 2003 (2003-08-07)

D4: WO 96/14334 A (COX LYNNE SUZANNE ;LANE DAVID PHILIP (GB); UNIV DUNDEE (GB); WARBR) 17 May 1996 (1996-05-17)

D5: WO 97/42222 A (LANE DAVID PHILIP ;CYCLACEL LTD (GB); BALL KATHRYN LINDSAY (GB)) 13 November 1997 (1997-11-13)

D6: WO 96/02140 A (SLOAN KETTERING INST CANCER ;KOFF ANDREW (US); MASSAGUE JOAN (US);) 1 February 1996 (1996-02-01)

D7: MONTAGNOLI E A: "Ubiquitination of p27 is regulated by Cd-dependent phosphorylation and trimeric complex formation" GENES AND DEVELOPMENT, COLD SPRING HARBOR LABORATORY PRESS, NEW YORK, US, vol. 13, no. 9, 1 May 1999 (1999-05-01), pages 1181-1189, XP002151561 ISSN: 0890-9369

D8: WO 02/090519 A (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 14 November 2002 (2002-11-14)

Re: III

For the assessment of the present claims 19 and 35, which (possibly) include *in vivo* diagnostic steps, on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may

allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re: V

1. Novelty

1.1 The applicant describes a p27Kip1 protein (hereafter p27), which is phosphorylated at the tyrosine residue at position 88, and which stimulates CDK4 activity. D1 and D2 each describe a p27 protein which activates/stimulates CDK4; see also first paragraph on page 3 of the description. The applicants themselves speculate that these results may be explained by the fact that the p27 protein used may be phosphorylated at tyrosine residue 88. The protein claimed in present claims 1 and 2 is therefore known from the prior art, or in any case indistinguishable from the prior art peptide. Although the prior art does not refer to tyrosine phosphorylation of the p27 protein, the discovery of this feature represents merely a further characterization of an apparently known protein, but that does not make the protein new in the sense of Art.33(2) PCT.

The applicant has argued that the results obtained in D1 and D2 are controversially discussed in the field and open to different explanations. At the time of publication of these prior art documents, that would indeed appear to be the case. However, it is the teaching of the present application that the p21 family of CDK inhibitors require phosphorylation in order to become active inhibitors. It therefore follows that the proteins described in D1 and D2 were in fact phosphorylated, since they did in fact poses inhibitory activity. The fact that the authors of this prior art did not know exactly what it was they held in their hands is not relevant for novelty; what they describe is in fact identical and indistinguishable from what is presently claimed, and that is therefore not new. The discovery by the applicant that these proteins are in fact phosphorylated before they can assume their physiological role may well have practical applications, and would appear not to be obvious. However, that has no bearing on the assessment of the compound per se in light of the prior art, which already disclosed it.

1.2 The previous novelty objections regarding claims 5, 6 and 8 are withdrawn in light of the applicants comments.

2. Inventive step and industrial applicability

The previous objections are withdrawn.

Re: VII

3. Disclosure, clarity and support

3.1 It would appear that p27 and p21, at least, can take over each others physiological role in a redundant fashion. Given the degree of identity in the conserved regions of these proteins, also compared to p57, it is likely that they function via the same or a similar mechanism. Furthermore, the skilled person can assess through routine experimentation, for which suitable protocols are provided in the application, whether in fact they do. The subject-matter of the present claims can therefore be considered to be sufficiently disclosed in respect of all three family members. The previous objections are withdrawn.

3.2 Claim 3 in fact does specify that the peptides must be phosphorylated, contrary to previous assertions by the IPEA. The objection as previously raised is therefore withdrawn.

3.3 The variant or peptidomimetic of claim 7 is however still dependent on claims 1 and 2. Variants or peptidomimetics of these known proteins are not considered inventive in the sense of Art.33(3) PCT.

3.4 The amendment is considered to overcome the previous objection to claim 9. Receipt of the proof of deposits is acknowledged for the hybridoma lines of claim 13.

Re: VIII

Claims 19 and 35 partially relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).